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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,495	02/28/2002	Chihiro Kusunoki	SHIMO13	2089

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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
LIETO, LOUIS D	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 08/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,495	KUSUNOKI ET AL.	
	Examiner	Art Unit	
	Louis D Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-14 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-14 is/are rejected.

7)☒ Claim(s) 5-14 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to comply*.

DETAILED ACTION

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2), see for example page 23, SEQ ID NO: 1. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures which is attached to this communication. Specifically, the CRF and the paper listing SEQ ID NO: 1 were not submitted in the instant application

APPLICANT IS GIVEN A THREE MONTH EXTENDABLE PERIOD WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of this application under 37 CFR 1.821 (g). Extension of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Applicant is requested to return a copy of the attached Notice To Comply with the response.

Specification

The specification on page 20 lists figures 1 and 2 in the brief description of the drawings. However, the application does not contain these drawings. Applicant is required to remove all

references to the missing drawings. See MPEP 601.01(g). Alternatively applicant may file a petition under 37 CFR 1.53(e). The petition fee will be refunded if it is determined that the drawings were in fact received by the USPTO with the application papers deposited on filing. An applicant desiring to submit any omitted drawings in a nonprovisional application must accept the date of such submission as the application filing date (see MPEP 601.01(g)).

Claim Objections

Claims 5-14 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only and cannot depend from any other multiple dependent claims. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The specification does not enable a method for producing a monoclonal antibody from "any cell " comprising a rearranged endogenous immunoglobulin heavy chain and a rearranged endogenous immunoglobulin light chain. The only cells recognized in the art to undergo somatic

rearrangement of the endogenous immunoglobulin heavy chain and light chain loci, and to secret an antibody, are B-cells {Abbas et al., (1994) Cellular and Molecular Immunology 2nd ed., 1-457; pg. 75, col. 2, pgph 3}. Claim 1 reads on all cells, such as T cells, fibroblasts, keratinocytes, etc. None of these cells are known in the art to comprise a rearranged endogenous immunoglobulin heavy chain and a rearranged endogenous immunoglobulin light chain and secret an antibody. The specification discloses B-cell hybridomas. The specification does not teach how to identify, isolate or produce non- B cells that comprise a rearranged endogenous immunoglobulin heavy chain, a rearranged endogenous immunoglobulin light chain and secret an antibody. Given the lack of guidance in the specification and the current teachings in the art a skilled practitioner would be unable to determine how to perform the invention with any cell other than a B cell, without arduous and extensive experimentation.

The specification does not enable a method for producing a monoclonal antibody from a hybridoma comprising a rearranged endogenous immunoglobulin heavy chain and a rearranged endogenous immunoglobulin light chain derived from any transgenic non-human mammal that produces a human antibody. At the time of filing, only transgenic mice had been engineered to contain endogenous human and heavy light chains that undergo B cell specific rearrangement and produce human antibodies, e.g. xenomouse II {Mendez et al., (1997) Nature Genetics. 15:146-186; pg, 146, Abstract; pg. 147, col. 1, pgph 2}. Claim 7 reads broadly on all non-human mammals, such as, zebras, dolphins, kangaroos, etc. None of these non-human mammals were described in the art, at the time of filing, as being transformed so that they can produce a human antibody resulting from endogenous recombination. Green et al. points out that even in mice the goal of constructing a transgenic mouse able to generate antigen specific human antibodies

proved elusive until 1994 {Green et al. (1994) Nature Genetics 7:13-21}. The specification is enabled for B-cell hybridomas from transgenic mice that produce human antibodies from endogenous human and heavy light chains that undergo recombination. However, the specification does not provide guidance on the manufacture of other transgenic non-human mammals that contain endogenous human and heavy light chains, undergo rearrangement and produce a human antibody. In addition, the art of making transgenic non-human mammals was considered unpredictable at the time of filing. Wells et al., reported that three of the commonly used techniques for producing transgenic animals had a variety of potential problems making their chances of success unpredictable {Wells et al. (1999) Nature Biotechnology. 17:25-6}. Specifically, Wells et al. pointed out technique specific difficulties, such as the fact that pronuclear microinjection were relatively inefficient, retrovirally transferred genes often did not function after integration and somatic cell nuclear transfer suffered from a very low fetal survival rate (Wells et al., pg. 25, Table 1). Thus, based on the unpredictability of generating transgenic non-human mammals at the time of filing, and the complete lack of guidance in the specification concerning the constructs and methods required to generate transgenic animals, the lack of working examples, and the breadth of the claims, it would have required undue experimentation to practice the invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent application No. US 2003/0153039 (8/14/2003), hereafter referred to Wood[1] et al., **or** US Patent No. 6,475,787 (11/5/2002), hereafter referred to Wood[2] et al., in view of Mendez et al. {Mendez et al., (1997) Nature Genetics. 15:146-186}.

Wood[1] et al. teaches a method for producing a monoclonal antibody by introducing into a hybridoma containing an exogenous rearranged immunoglobulin heavy chain and an exogenous rearranged immunoglobulin light chain, a third exogenous DNA corresponding to the DNA encoding the immunoglobulin heavy chain, the culturing of said cell and the production of a functional monoclonal antibody (Wood[1] et al., pg. 5, col. 2, claims 4,5 and 6). Specifically, Wood et al., teaches a mammalian B-cell hybridoma comprising DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain (Wood[1] et al., pgph 0013; pgph 0021; Wood[2] et al., col. 3, section II col. 4, pgph 3) and the introduction of a DNA encoding the identical immunoglobulin heavy chain (Wood[1] et al, pgph 0024; Wood[2] et al, col. 5, pgph 1). Wood et al. provides guidance that the DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain can be from any animal, which includes humans as well as non-human mammals, as well as genetically engineered chains that would comprise a mouse-human fusion antibody (Wood[1] et al., pgph 0010; pgph 0012; Wood[2] et al., col. 2, pgph 4; col. 3, section I). Further, Wood et al. teaches that the DNA encoding the immunoglobulin heavy chain comprises an amplifiable marker such as dihydrofolate reductase (DHFR) (Wood[1] et al., pgph 0007; Wood[2] et al., col. 2, pgph 1). Wood et al. teaches the culture of said cells and measurement of the monoclonal antibody (Wood[1] et al., pg. 4, examples 3 and 4; Wood[2] et al., col. 7&8,

examples 3 and 4). Wood et al. teaches that the object of the invention is to improve the levels of antibody expression (Wood[1] et al., pgph 0006; Wood[2] et al., col. 1, pgph 6), specifically through the optimization of heavy chain gene copy numbers (Wood[1] et al., pgph 0008; Wood[2] et al., col. 2, pgph 2). Wood et al. does not teach that the cell is derived from a transgenic non-human mammal or that it contains endogenous immunoglobulin heavy and light chains that encode a secreted antibody.

Mendez et al., supplements the teachings of Wood[2] et al. by providing guidance on a transgenic mouse containing endogenous human DNA encoding heavy and light chains that undergo B cell specific rearrangement and produces human antibodies (Mendez et al., pg. 146, col. 2 pgph 2). Further, Mendez et al. teaches transgenic mouse B cell hybridomas (Mendez et al., pg. 151, col. 1 pgph 2).

Based on the motivation of Wood et al. that the antibody production of B cell hybridomas can be increased by transfecting them with an immunoglobulin heavy chain it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to apply the teachings of Wood et al. to any b-cell hybridomas with endogenous rearranged heavy and light chains including the transgenic mouse B cell hybridoma taught by Mendez et al.

The person of ordinary skill in the art would have been motivated to make this modification in order to increase the antibody production of B cell hybridomas and would reasonably be expected to succeed because Wood et al. has shown that this method works to increase antibody production in mammalian cells, which contain an immunoglobulin heavy chain and an immunoglobulin light chain.

No claims are free of the prior art of record.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Amy J Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is (703)-872-9306. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Louis D. Lieto, Ph.D.
Patent Examiner
Art Unit 1632

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER

Application No.: 09/937,495

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- [X] 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- [X] 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- [X] 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- [ ] 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- [ ] 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- [ ] 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- [ ] 7. Other: _____

Applicant Must Provide:

- [X] An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- [X] An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- [X] A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

PLEASE RETURN A COPY OF THIS NOTICE WITH YOUR RESPONSE